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An Alternative Synthesis of 1,1′-Bis-valienamine from D-Glucose

Tony K. M. Shing* and Hau M. Cheng

Department of Chemistry and Center of Novel Functional Molecules, The Chinese University of Hong Kong, Shatin, Hong Kong

tonyshing@cuhk.edu.hk

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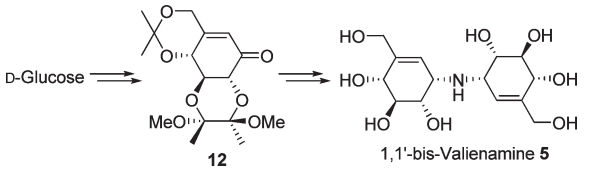

An alternative synthesis of 1,1′-bis-valienamine **5**, which was demonstrated to be a potent trehalase inhibitor, has been achieved from D-glucose in 12 steps with 15% overall yield via enone **12** as the key intermediate, involving a direct aldol reaction of a glucose-derived diketone and a palladium-catalyzed allylic coupling reaction as the key steps.

Sugar-mimicking glycosidase inhibitors as potential antidiabetic, anticancer, and antiviral agents have stimulated great demand of these compounds for biological studies.[1] Immense efforts have been dedicated to the construction[2−4] of α-D-glucosidase inhibitor valienamine (**1**)[2] since its isolation[5] in 1972. Valienamine (**1**) is an essential core unit in many kinds of pseudo-oligosaccharidic α-D-glucosidase inhibitors such as methyl acarviosin (**2**) and acarbose (**3**) (Figure 1).[6] The constitution of 1,1′-*N*-linked-pseudodisaccharide **5**, i.e., 1,1′-bis-valienamine, resembles trehalose (**4**) (1,1′-bis-α-D-glucose) structurally and has been shown to be a strong and specific inhibitor (IC_{50} 1.7×10^{-8} M)[7] against trehalase[8] and, therefore, has the potential to be developed as a human-safe insecticide.

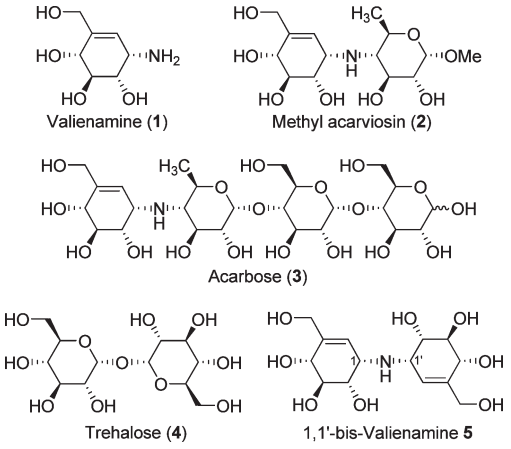

FIGURE 1. Valienamine and its related compounds.

A few years ago, we published a facile, regio- and stereospecific synthesis of 1,1′-bis-valienamine **5** in 16 steps from (−)-quinic acid with an overall yield of 12%.[7] This 1,1′-*N*-linked-pseudodisaccharide **5** was demonstrated to be a potent trehalase inhibitor and was assembled by a key palladium-catalyzed coupling reaction of 2,3:4,6-diacetonated allylic chloride **6** and allylic amine **7**, both of which were transformed from allylic alcohol **8** (Scheme 1).[7] However, during the palladium-catalyzed coupling reaction, an undesirable *β*-hydride elimination to alleviate the *trans*-isopropylidene ring strain in the allylic chloride **6** to give diene **9** was a competitive reaction against the nucleophilic substitution with the allylic amine **7**. Hence, dropwise addition of the allylic chloride **6** into a mixture of an excess amount (ca. 4 equiv) of the precious amine **7** and the palladium complex was required in order to attain a good chemical yield (78%).[7] However, the drawback of this protocol is the need of a much larger quantity of the allylic amine **7** and the laborious recovery of the unreacted **7** by chromatography.

The great demand of **5** for detailed biological evaluation and the high cost of (−)-quinic acid as the starting material prompted us to investigate a shorter, more efficient, and economical synthetic route. This paper describes an efficient construction of 1,1′-bis-valienamine **5** from cheap and readily available D-glucose using an intramolecular aldol cyclization of a diketone and a palladium-catalyzed allylic coupling reaction as the key steps.

Our endeavors in amino pseudosugar synthesis from D-glucose have already produced pseudoacarviosin,[9] valiolamine, and validoxylamine G.[10] The present paper further demonstrates the versatility of this avenue for the efficient

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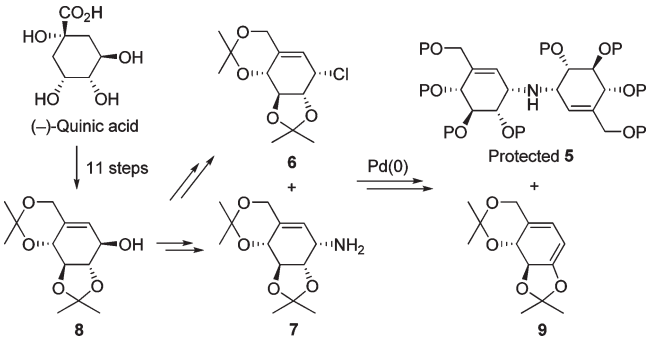
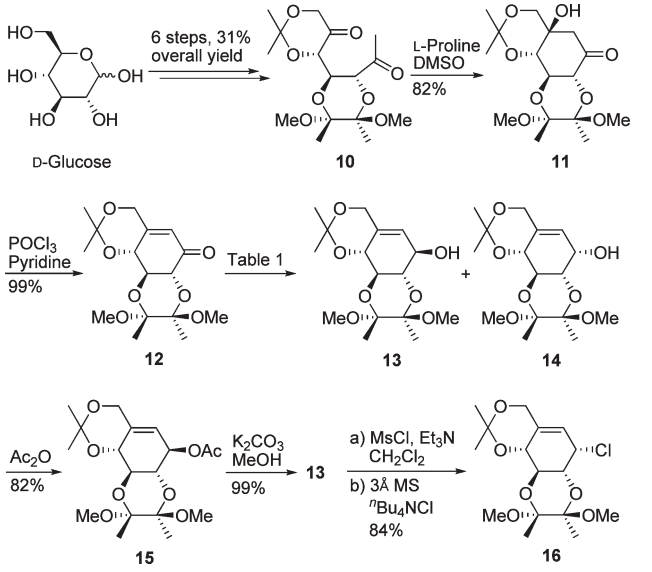
SCHEME 1. Previous Synthesis of 1,1′-Bis-valienamine 5 from (−)-Quinic Acid via Allylic Alcohol 8.[7]



SCHEME 2. Preparation of Allylic Chloride 16 from D-Glucose[9,10]



synthesis of 1,1′-bis-valienamine (**5**) via enone **12** as the key intermediate.

In our previous investigation on the construction of carbocycles from carbohydrates, diketone **10** (prepared from D-glucose in 6 steps with 31% overall yield) was employed to undergo the intramolecular aldol cyclization to give enone **12** (Scheme 2).[9,10] Attempts toward regio- and diastereoselective 1,2-reduction of enone **12** were investigated, and the results are shown in Table 1. The best conditions for the formation of β-alcohol **13** was sodium borohydride reduction assisted by cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) at −30 °C, affording a mixture of inseparable allylic alcohols **13** and **14** in a 5:1 ratio, respectively (entry 4).[11] The β-alcohol **13** proved difficult to obtain pure by chromatography, but its corresponding acetate **15** was readily isolated clean and was converted smoothly into α-allylic chloride **16** as reported previously by us.[9]

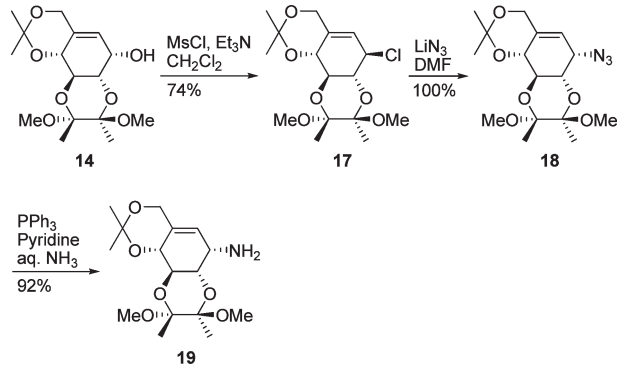
On the other hand, exclusive formation of α-alcohol **14** from enone **12** was feasible with K-Selectride in excellent yield (entry 7).

TABLE 1. Reduction of Enone 12 to Allylic Alcohols 13 and 14

entry	conditions	ratio of **13**:**14**[a]	yield (%)
1	$NaBH_4$, MeOH, 0 °C	1:1	98
2	$NaBH_4$, MeOH, −10 °C	1:1	97
3	$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −10 °C	4:1	99
4	$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −30 °C	5:1	99
5	$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C	5:1	98
6	DIBAL-H, THF, −78 °C to rt	5:1	98
7	K-Selectride, THF, −78 °C	0:1	99

[a]Ratio was determined by ^{1}H NMR spectroscopy.

SCHEME 3. Synthesis of Amine 19



The synthesis of the coupling donor, the acetal protected valienamine **19**, is shown in Scheme 3. The allylic α-alcohol **14** was esterified with mesyl chloride. The resultant mesylate was too unstable to be isolated but reactive enough to be displaced by the chloride ion formed in situ to give allylic chloride **17** in one pot. The allylic β-chloride **17** was readily displaced with LiN_3 to afford allylic α-azide **18** in a quantitative yield. Staudinger reduction[12] of the azide **18** with triphenylphosphine/aqueous ammonia furnished the desired coupling partner α-allylic amine **19** in an excellent yield without incident.

Palladium-catalyzed coupling reaction[13] of allylic chloride **16** with amine **19** produced 1,1′-*N*-linked pseudodisaccharide **20** in an excellent yield. The cis-orientation of NH-1 and OR-2 in adduct **20** is evident from the coupling constants ($J_{1,2}$ = 4.8; $J_{2,3}$ = 10.8 Hz), and thus, the coupling reaction occurred with retention of configuration of the allylic α-chloride **16** (Scheme 4). From our experience, an excess amount (ca. 2 equiv) of the nucleophilic amine **19** should be used to ensure a rapid reaction and suppress the formation of a diene side product.[8] Fortunately, under these conditions, no sign of an elimination diene related to **9** was observed. Acidic hydrolysis then afforded the target molecule 1,1′-*N*-linked pseudodisaccharide **5**.[7,8,14] The ^{1}H and ^{13}C NMR spectral data of 1,1′-bis-valienamine **5** are in agreement with those in the literature,[8] and the specific rotation value was found to be consistent with that reported recently.[14] One reviewer inquired

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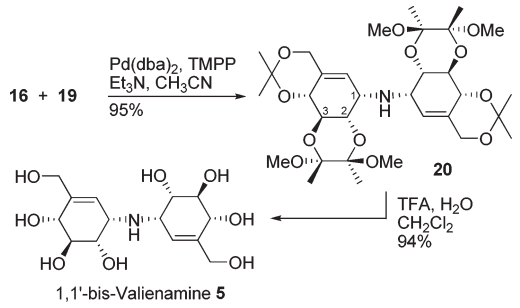
SCHEME 4. Synthesis of 1,1′-Bis-valienamine 5



about the feasibility of the conversion of allylic alcohol **14** into chloride **16**, which would render the synthesis more efficient. We reckon that this is feasible. The configuration of the free α-alcohol in **14** could be inverted by Mitsunobu reaction followed by de-esterification and chlorination to give *β*-chloride **16**. Research in this direction is in progress.

To conclude, 1,1′-bis-valienamine **5** was synthesized from D-glucose in 12 steps with 15% overall yield involving enone **12** as the key intermediate. This route offers improvement over our previous endeavor in terms of a shorter sequence and with a higher overall yield. Furthermore, in the key palladium-catalyzed allylic substitution, we have successfully reduced the amount of amine **19** from 4 to ca. 2 equiv, which enables the protocol to be more efficient and convenient. The change of the 2,3-*O*-acetonide group in allylic chloride **6** to the trans-diacetal blocking group in **16** obviously renders the chloride **16** stability to avoid the undesirable *β*-hydride elimination. The use of cheap and virtually inexhaustible starting material D-glucose as oppose to quinic acid is also noteworthy.

Experimental Section

1,1′-Bis-valienamine 5. To a solution of amine **20** (56.7 mg, 0.088 mmol) in CH_2Cl_2 (5 mL) were added trifluoroacetic acid (TFA) (0.5 mL) and water (0.05 mL) at room temperature. The resultant solution was stirred for 4 days at room temperature. Concentration of the solution followed by flash chromatography ($CHCl_3$:MeOH, 2:1) yielded 1,1′-bis-valienamine **5** (27.7 mg, 94%) as a colorless oil: $[\alpha]^{20}_D$ +148 (*c* 0.38, MeOH) [lit.[14] $[\alpha]^{20}_D$ +143.9 (*c* 0.2, MeOH)]; R_f = 0.29 ($CHCl_3$/MeOH/32% aq NH_3, 1.6:1.2:0.6);[8] ^{1}H NMR (400 MHz, CD_3OD) *δ* 3.65−3.75 (m, 4H), 3.73 (dd, *J* = 8.1, 6.1 Hz, 2H), 3.96 (d, *J* = 6.0 Hz, 2H), 4.17 (t, *J* = 15.3 Hz, 2H), 3.88 (t, *J* = 1.5 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) *δ* 53.6, 61.8, 69.1, 71.0, 72.7, 119.9, 141.8; *m*/*z* (ESI) 334 ([M + H]$^+$, 100); HRMS (ESI, [M + H]$^+$) found 334.1498, calcd for $C_{14}H_{23}NO_8$ 334.1496.

Alcohol 14. To a solution of the enone **12** (2.01 g, 6.12 mmol) in THF (35 mL) at −78 °C was added 1 M THF solution of K-Selectride (9 mL, 9 mmol) over 30 min, and the mixture was stirred for 12 h at room temperature. The reaction was quenched with saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (*n*-hexane/EtOAc, 1:1) gave α-alcohol **14** (2.00 g, 99%) as a colorless oil: $[\alpha]^{20}_D$ −118 (*c* 1.51, $CHCl_3$); R_f = 0.33 (*n*-hexane/EtOAc, 1:1); IR (thin film) 3469, 2994, 2950, 1645, 1455, 1376, 1140, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.33 (s, 6H), 1.38 (s, 3H), 1.49 (s, 3H), 3.27 (s, 6H), 3.62 (dd, *J* = 11.1, 4.2 Hz, 1H), 4.06 (dd, *J* = 11.1, 8.1 Hz, 1H), 4.14−4.22 (m, 2H), 4.38−4.43 (m, 2H), 5.59 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 18.1 (CH_3), 18.2 (CH_3), 20.8 (CH_3), 28.3 (CH_3), 48.4 (CH_3), 48.6 (CH_3), 63.2 (CH_2), 65.6 (CH), 67.2 (CH), 68.3 (CH), 70.3 (CH), 99.4 (C), 99.7 (C), 100.1 (C), 119.6 (CH), 136.8 (C); *m*/*z* (ESI) 353 ([M + Na]$^+$, 100); HRMS (ESI, [M + Na]$^+$) found 353.1579, calcd for $C_{16}H_{26}O_7$ 353.1571.

Allylic Chloride 17. To a solution of the α-alcohol **14** (177 mg, 0.536 mmol) in CH_2Cl_2 (8 mL) and Et_3N (0.45 mL, 3.22 mmol) was added methanesulfonyl chloride (MsCl) (0.13 mL, 1.68 mmol) at 0 °C. The mixture was stirred for 7 days at room temperature. The mixture was then filtered through a thin pad of silica gel topped with Celite, and the residue was washed with diethyl ether until no product was observed in the eluent (checked with TLC). Concentration of the filtrate followed by flash chromatography (*n*-hexane/Et_2O, 3:1) yielded allylic chloride **17** (139 mg, 74%) as a colorless oil: $[\alpha]^{20}_D$ −252 (*c* 0.62, $CHCl_3$); R_f 0.53 (*n*-hexane/Et_2O, 1:1); IR (thin film) 2937, 1355, 1174 cm^{-1}; IR (thin film) 2951, 2912, 1457, 1380, 1135, 1034, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.33 (s, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.51 (s, 3H), 3.27 (s, 3H), 3.33 (s, 3H), 3.77 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.85 (dd, *J* = 10.8, 8.4 Hz, 1H), 4.10 (d, *J* = 13.2 Hz, 1H), 4.47 (d, *J* = 12.9 Hz, 1H), 4.56 (d, *J* = 8.1 Hz, 1H), 5.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 18.0 (CH_3), 20.3 (CH_3), 28.7 (CH_3), 48.5 (CH_3), 57.5 (CH), 63.1 (CH_2), 69.6 (CH), 71.2 (CH), 72.9 (CH), 99.4 (C), 99.7 (C), 99.8 (C), 121.5 (CH), 133.7 (C); *m*/*z* (ESI): 371 ([M + Na]$^+$, 100); HRMS (ESI, [M + Na]$^+$) found 371.1246, calcd for $C_{16}H_{25}ClO_6$ 371.1232.

Azide 18. To a solution of the allylic chloride **17** (115 mg, 0.329 mmol) in DMF (4 mL) was added LiN_3 (115 mg, 0.329 mmol) at room temperature. The resultant solution was stirred for 3 h at 80 °C. The mixture was then cooled to 0 °C, diluted with EtOAc (10 mL), washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (*n*-hexane/Et_2O, 1:1) gave azide **18** (119 mg, 100%) as a colorless oil: $[\alpha]^{20}_D$ −24.7 (*c* 0.71, $CHCl_3$); R_f = 0.37 (*n*-hexane/Et_2O, 1:1); IR (thin film) 2993, 2949, 2111, 1456, 1375, 1137 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.32 (s, 3H), 1.34 (s, 3H), 1.38 (s, 3H), 1.49 (s, 3H), 3.27 (s, 3H), 3.29 (s, 3H), 3.80 (dd, *J* = 10.8, 4.5 Hz, 1H), 4.00 (dd, *J* = 11.1, 8.1 Hz, 1H), 4.11−4.16 (m, 2H), 4.37−4.41 (m, 2H), 5.47 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 17.9 (CH_3), 18.2 (CH_3), 20.7 (CH_3), 28.3 (CH_3), 48.5 (CH_3), 48.6 (CH_3), 57.8 (CH), 63.1 (CH_2), 67.7 (CH), 68.2 (CH), 70.3 (CH), 99.3 (C), 99.8 (C), 100.1 (C), 116.6 (CH), 137.6 (C); *m*/*z* (ESI): 353 ([M + Na]$^+$, 100); HRMS (ESI, [M + Na]$^+$) found 378.1639, calcd for $C_{16}H_{25}N_3O_6$ 378.1636.

Amine 19. To a solution of the azide **18** (120 mg, 0.338 mmol) in pyridine (3 mL) and aqueous NH_3 (32%, 2 mL) was added PPh_3 (176 mg, 0.672 mmol), and the mixture was stirred for 24 h at room temperature. The resultant solution was diluted with EtOAc (10 mL) and washed with brine (2 × 5 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. Concentration of the filtrate followed by flash chromatography ($CHCl_3$/MeOH, 30:1) gave amine **19** (102 mg, 92%) as a colorless oil: $[\alpha]^{20}_D$ −86.2 (*c* 0.32, $CHCl_3$); R_f = 0.33 ($CHCl_3$/MeOH, 20:1); IR (thin film) 3377, 2992, 2917, 1456, 1134, 1035 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) *δ* 1.29 (s, 3H), 1.31 (s, 3H), 1.33 (s, 3H), 1.53, (s, 3H), 3.24 (s, 3H), 3.27 (s, 3H), 3.39 (t, *J* = 4.8 Hz, 1H), 3.64 (dd, *J* = 11.4, 5.1 Hz, 1H), 3.93 (dd, *J* = 11.1, 8.1 Hz, 1H), 4.09 (d, *J* = 13.8 Hz, 1H), 4.45−4.52 (m, 2H), 5.57 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 18.2 (CH_3), 18.3 (CH_3), 20.2 (CH_3), 29.0 (CH_3), 48.4 (CH_3), 49.3 (CH), 63.7 (CH_2), 67.3 (CH), 68.0 (CH), 70.6 (CH), 99.3 (C), 99.5 (C), 99.8 (C), 122.9 (CH), 133.1 (C); *m*/*z* (ESI) 330 ([M + H]$^+$, 100); HRMS (ESI, [M + H]$^+$) found 330.1905, calcd for $C_{16}H_{27}NO_6$ 330.1911.

Amine 20. To a mixture of chloride **16** (49.2 mg, 0.141) and amine **19** (88.7 mg, 0.269 mmol) in CH_3CN (2 mL) was added

bis(dibenzylideneacetone)palladium(0) (4.1 mg, 0.007 mmol), TMPP (3.4 mg, 0.02 mmol), and Et_3N (0.1 mL, 0.717 mmol). The resultant solution was stirred for 48 h at room temperature under nitrogen. Concentration of the solution followed by flash chromatography gave first (hexane/Et_2O, 1:1.5) the protected 1,1′-bis-valienamine **20** (86.0 mg, 95%) as a colorless oil and ($CHCl_3$/MeOH, 30:1) second the starting amine **19** (39.1 mg). Data for **20**: $[\alpha]^{20}_D$ +23.6 (*c* 0.39, $CHCl_3$); R_f = 0.35 (*n*-hexane/Et_2O, 1:3); IR (thin film) 3370, 2992, 2923, 1457, 1373, 1120, 1040, 756 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 1.23 (s, 3H), 1.36 (s, 3H), 1.37 (s, 3H), 1.54 (s, 3H), 3.10 (s, 3H), 3.20 (s, 3H), 3.84 (dd, J = 10.8, 4.5 Hz, 1H), 3.96 (brs, 1H), 4.03 (d, J = 13.5 Hz, 1H), 4.16 (d, J = 13.8 Hz, 1H), 4.33 (dd, J = 10.8, 7.8 Hz, 1H), 4.51 (d, J = 7.8 Hz, 1H), 5.80 (d, J = 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_3), 18.3 (CH_3), 20.4 (CH_3), 28.9 (CH_3), 48.4 (CH_3), 55.9 (CH), 63.7 (CH_2), 68.1 (CH), 69.6 (CH), 70.6 (CH), 99.1 (C), 99.3 (C), 122.8 (CH), 131.5 (C); *m*/*z* (ESI) 642 ($[M + H]^+$, 100); HRMS (ESI, $[M + H]^+$) found 642.3471, calcd for $C_{32}H_{51}NO_{12}$ 642.3484.

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Supporting Information Available: General procedure and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.